Chapter

Protic Reaction Media for Nucleophilic Substitution Reactions

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Abstract

This chapter deals with the unusual substitution reactions in non-aprotic solvent. Selective protic solvents that are widely being accepted for nucleophilic substitution reactions not only enhance the reaction rate but also give desire for selectivity of substituted product. Protic solvents such as *tert*-alcohol, primary alcohol, ionic liquids with *tert*-alcohol and primary alcohol functionality, and bis-cationic ionic liquid with protic functionality were shown best result in substitution reactions. Aliphatic nucleophilic substitution significantly developed in protic reaction medium due to the hydrogen bonding interaction with leaving groups and nucleophile. The development of substitution reactions from past two decades are summarised in this book chapter.

Keywords: substitution reactions, nucleophilic, alcohol solvents, phase transfer catalyst

1. Introduction

Substitution reaction is one of the important classes of organic reactions. The term substitution itself indicates that the organic reaction process in which the one moiety/functional group will be replaced by other new group/moiety. Generally, there are two types of substitution reactions: one is bimolecular substitution reaction and the other is unimolecular substitution (S_N1) reaction. The bimolecular reaction is a reaction in which the replacing group generates partially a positive charge on a substrate and a new electron-rich group occupies the position of the replacing group as shown in **Figure 1**. In short, it is referred as bimolecular nucleophilic substitution reactions (S_N2) [1]. Aliphatic nucleophilic substitution reaction is generally performed in a non-protic solvent so that the nucleophile will be free

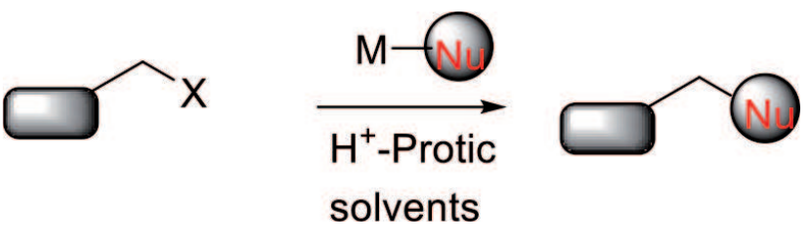

Figure 1.
Substitution reactions with metal nucleophile (MNu) in protic solvent.

and flexible to replace the leaving group. In case of a protic solvent, the electron-rich species of nucleophile forms the hydrogen bond; thus, it reduces the efficiency of nucleophile, decreases nucleophilicity, and reduces the reaction rate. By contrast, some reactive nucleophiles, which show duel characters, may act as a base as well as a nucleophile; in such case, the possibility to form other side products are more. To improve the selectivity of the product, hydrogen bonding with reactive nucleophile will play a key role. Thus, a number of nucleophilic substitution reactions are performed in protic solvents such as *tert*-butanol, alcohol-functionalized ionic liquids, ammonium ionic liquids, or polyethylene glycols. In this book chapter, the recent development of S_N2 reactions in protic solvent to improve the selectivity of substituted product is covered [2].

2. Protic solvent substitutions

2.1 Alcohol-mediated substitution reactions

Chi et al. developed the nucleophilic substitution reactions using *tert*-alcohol solvents such as *tert*-butanol, *tert*-amyl alcohol, etc [3]. Nucleophiles such as fluorine gave promising results and an excellent desire for the selectivity of fluorinated product with low formation of corresponding by-product alkene. **Figure 1** shows the alkyl sulfonate leaving group replaced by fluorine efficiently in the *tert*-amyl alcohol-mediated reaction conditions. The extreme effect of protic solvent-mediated fluorination with alkali metal fluoride was demonstrated.

They observed that the alcohol solvent particularly nonpolar such as *tert*-alcohol enhances the nucleophilicity of the electron-rich nucleophilic ion, radically in lack of any type of promoter or phase-transfer catalyst, which significantly enhances the rate of the nucleophilic substitutions and reduces the generation of corresponding side products, i.e. alcohols, ethers and alkene, compared with substitution reactions in dipolar aprotic medium. The importance of this reaction method is that it is useful in radiopharmaceuticals for the synthesis of fluorine-18-labelled imaging agents for positron emission tomography (PET) [4]. They demonstrated the application of protic-mediated reactions for radiolabelling of important molecular imaging agents in good yield and quality in shorter time compared to aprotic-mediated reaction conditions of nucleophilic substitution reactions [5]. They further studied the influence of the *tert*-alcohol solvent conditions for nucleophilic substitutions with series of alkali metal fluorides. The possible hydrogen bonding interaction of nucleophile fluorine and the sulfonyloxy substrate promote the rate of reaction [6]. Mechanistically, the hydrogen bonding between alkali metal fluoride and aprotic solvent, the generation of protic alcohol-solvated ion and the hydrogen bonding between the leaving group sulfonate and the alcohol solvent seem to favour the enhancement in the rate of nucleophilic substitutions without PTC. They found that the fluorination with specific substrates with *tert*-butylammonium fluoride in alcohol solvent affords the corresponding fluoroproducts in high yield than that obtained by the conventional methods using dipolar aprotic solvents. The protic medium also suppresses the formation of by-products, such as alkenes, ethers and cyclic adducts.

2.2 *Tert*-alcohol-functionalized ionic liquid

Shinde et al. exhibited the synergistic effect of *tert*-alcohol and ionic liquids in substitution reactions [7]. They merged the two solvents, ionic liquid (IL) and *tert*-alcohols, into one molecule for nucleophilic substitution as shown in

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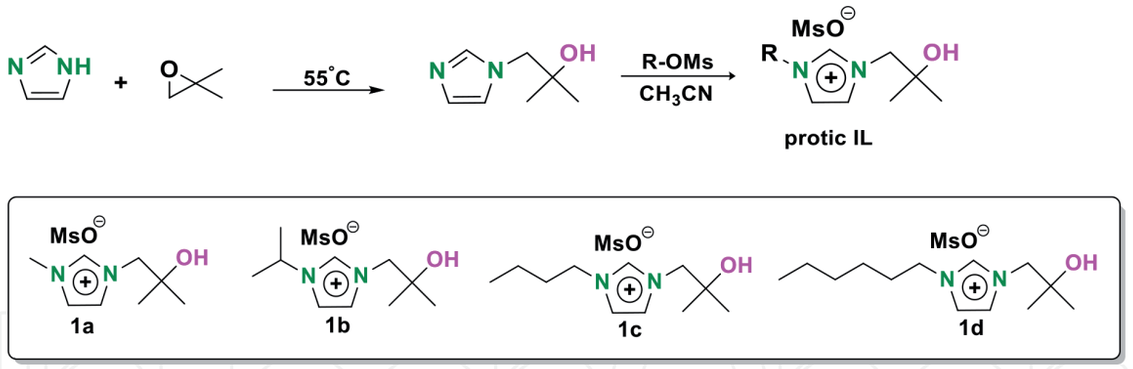


Figure 2.
Synthesis of tert*-alcohol-functionalized ionic liquid for substitution reactions.*

Figure 2. These hybridised ILs not only increase the nucleophilic reactivity of the fluoride anion but also reduce the olefin by-product. The preparation of novel imidazolium salts with counter anion [8]. Imidazole reacted with isobutylene oxide without or free solvents to give quantitatively yield N-*tert*-alcohol-substituted imidazole. N-*tert*-alcohol-substituted imidazole reacted with methyl, isopropyl, n-butyl, n-hexyl methane sulphonate in acetonitrile at 90°C gave the corresponding N_1-alkyl-N_3-*tert*-alcohol substituted imidazolium salts (ILs) **1a–1d.** All of these imidazolium mesylates are liquids at room temperature.

In the development of the fluorination process, ILs play both roles, i.e. reaction media and phase-transfer catalysts. They found that nucleophilic fluorination is accelerated in **1a** and that *tert*-alcohol solvents show good performance in nucleophilic fluorination, thereby side reactions are remarkably suppressed via a weak F**–**H hydrogen bond, which maintains the inherent nucleophilicity and reduces the basicity of the fluoride anion. The new hybridization of ILs and *tert*-alcohol functionality would provide dual advantages of reaction acceleration and minimization of side reactions.

Figure 3 depicted the use of protic ionic liquid in nucleophilic fluorination. The reaction of the primary triflate of R-D-galactopyranose in the presence of **1a** as a protic catalyst yielded the fluorinated product (**6a**) in almost quantitative yield with no by-products [7].

The reaction of the secondary mesylate, which could easily be eliminated to the corresponding olefin, showed a similar trend. Such superior reactivity and selectivity were obviously due to the previously mentioned synergistic effect of *tert*-alcohol functionality and imidazolium salts (**Figure 4**) [9].

2.3 Protic ethylammonium nitrate

Crosio et al. developed a new protic ionic liquid (IL) ethylammonium nitrate (EAN) inside toluene/benzyl-n-hexadecyldimethylammonium chloride (BHDC) as shown in **Figure 5** and studied its application on reverse micelles affects [10]. They found the Cl ion nucleophilicity on the bimolecular nucleophilic substitution (S_N2) reaction between this anion and dimethyl-4-nitrophenylsulfonium trifluoromethanesulfonate. It was the first study where the polar EAN was used as a suitable reaction medium for toluene-BHDC reverse micelles as a nanoreactor for performing the kinetic studies. The light scattering experiment discloses the formation of RMs containing the protic EAN ionic liquid component. Their experiments demonstrate that the homogeneous reaction medium is low effective compared to EAN-mediated S_N2 reaction conditions. The protic ionic liquid EAN acts as a aprotic medium once it is entrapped in BHDC RMs by hydrogen bonding

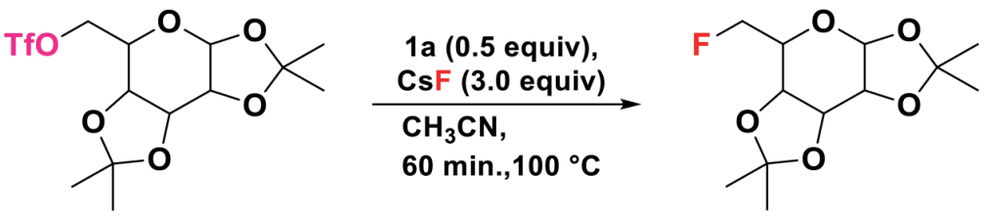
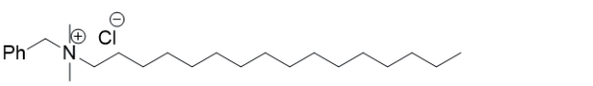
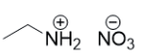


Figure 3.
Nucleophilic fluorination by protic ionic liquid ***1a****.*

Figure 4.
Nucleophilic fluorination on secondary mesylate by using CsF and ***1a****.*



benzyl-n-hexadecyldimethylammonium chloride (BHDC)



ethylammonium nitrate (EAN)

Figure 5.
Structures of ethylammonium nitrate (EAN).

interactions; as a result, nucleophilicity of chloride increases dramatically. Thus, the protic EAN is found as a suitable reaction solvent for nucleophilic bimolecular substitution reactions. These experiments demonstrate the flexibility of this kind of nanoreactor system to alter the polar protic solvent trapping and its impact on the rate of the reaction.

2.4 Polar protic solvent glycol

Song et al. observed that the alcohol contained polyethylene glycol as good reaction media for various nucleophilic substitution reactions [10]. Achiral polyether derivatives have shown dramatic acceleration in the S_N2 reactions by the simultaneous activation of both the nucleophile and electrophile sites of the leaving group. They also studied desiylation and found that bis-terminal –OH group plays a key role that the desilylative kinetic resolution is successively done of the silyl ethers of racemic secondary alcohols.

2.5 Primary alcohol-functionalized ionic liquid

Further, polyethylene glycol was used for functionalization of imidazolium-based ionic liquid and studied for S_N2 reactions. Kim et al. [12] synthesised hexaehtylene glycol *chain IL*s [hexaehtylene glycol-im][OMs] and [dihexaehtylene glycol-im][OMs] (hexaehtylene glycol-im = 1-hexaethylene glycolic 3-methylimidazolium cation; dihexaehtylene glycol-im = 1,3-dihexaethylene glycolic imidazolium cation; OMs = mesylate anion) by using simple organic reaction process as shown in **Figure 6** [11]. Synthesized various lengths of oligoether was have better chelation efficiency with metal cation due to presence of oxygen atoms intraction from both side of imidazolium IL.

The author described the role of all functional moieties of ionic liquid in nucleophilic fluorination by using salts of metal nucleophiles (**Figure 7**).

The application of di-functional polyether chain-substituted imidazolium ionic liquids in the synthesis of various bioactive molecules such as fluoro-flumazenil, fluoropropyl ciprofloxacin, etc., which are useful in molecular probes for PET, is synthesised using a protic ionic liquid as shown in **Figure 8**.

2.6 Di-*tert*-alcohol-functionalized dicationic ionic liquid

The same research group developed another dicationic protic ionic liquid for substitution reactions. A task-specific hexaethylene glycol bridged bis-cationic ionic liquid (BFIL) such as bis(2-hydroxy-2-methyl-n-propylimidazolium) dimesylate (hexaehtylene glycol chain-D^{t}OHIM) was prepared, and its role in nucleophilic substitution reactions using an alkali metal nucleophiles was investigated [13]. They also compared their activities with a variety of mono-cationic ILs and found that the hexaehtylene glycol chain-functionalized IL more effectively enhanced the reactivity of KX compared with the *tert*-alcohol-functionalized IL hexaehtylene glycol chain-D^{t}OHIM (**Figure 9**).

The use of bis-functionalized ionic liquid (BFIL) enhances the substitution reaction rate compared to conventional ionic liquid as well as mono-functionalized protic ionic liquid due to the higher activity of BFIL by the additional dicationic moieties compared with the mono-cationic ionic liquid methods. The author found that the hexaethylene glycol moiety of these hexaehtylene glycol chain-functionalized ILs enhances the reactivity of alkali metal fluorides by two effects; one is chelation effect with alkali metal cations, allowing the fluoride to become necked, and the other is the flexible fluoride influence by flexible H-bonding between the hydroxyl groups of BFIL, t-alcohol medium and nucleophile. In the case of t-alcohol-functionalized BFIL, the t-alcohol moiety showed selectively flexible H-bonding in the process. Subsequently,

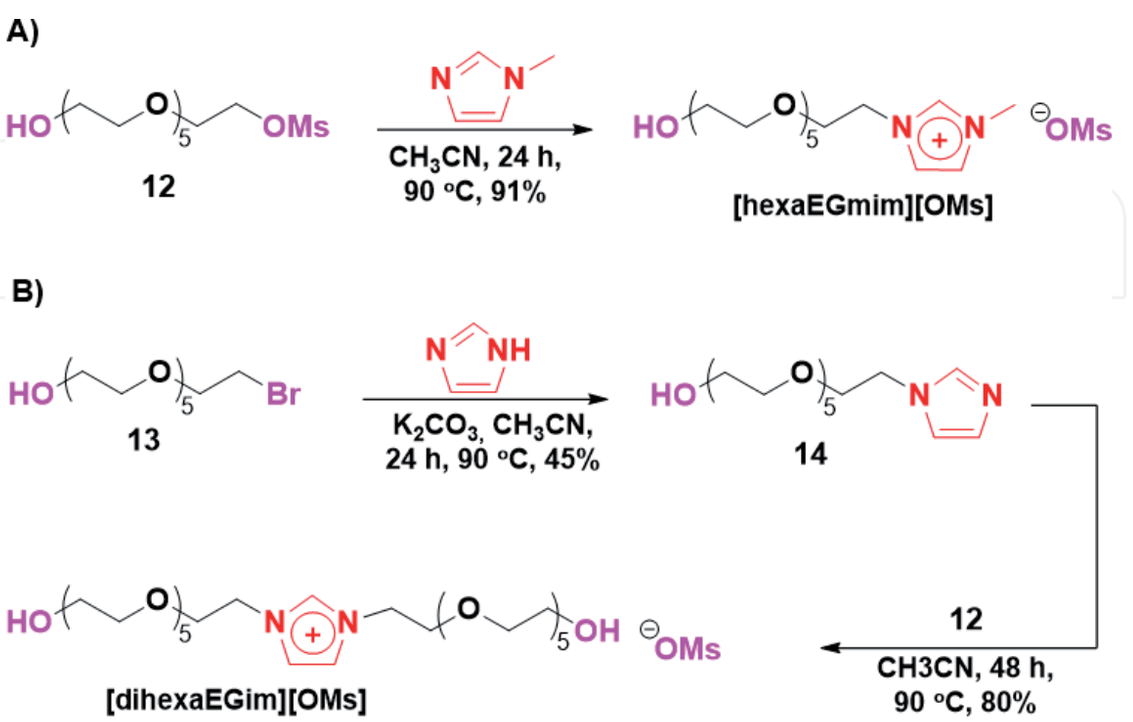


Figure 6.
Synthesis of polar-aprotic glycol substituted imidazolium ionic liquids. A) mono-glycol chain substituted IL, B) bis-glycol chain substituted IL.

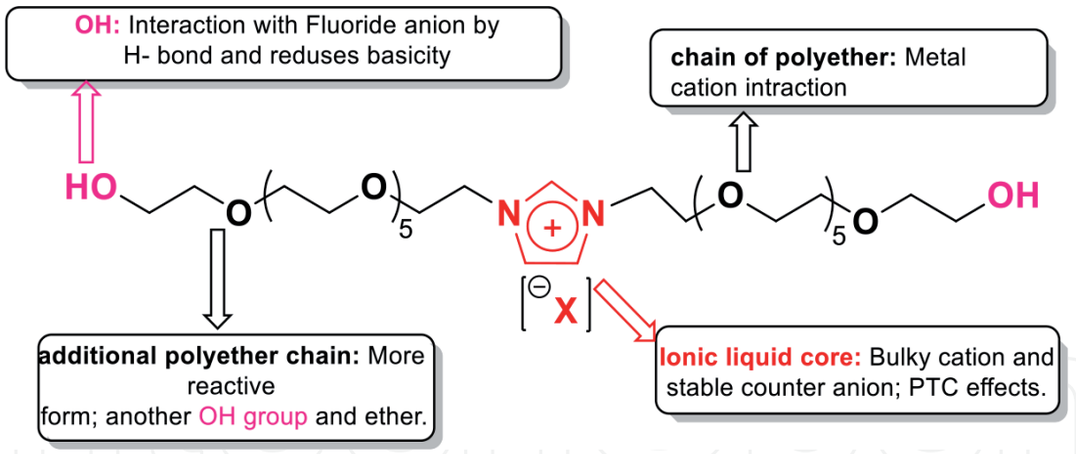


Figure 7.
Di-functional polyether chain-substituted imidazolium IL.

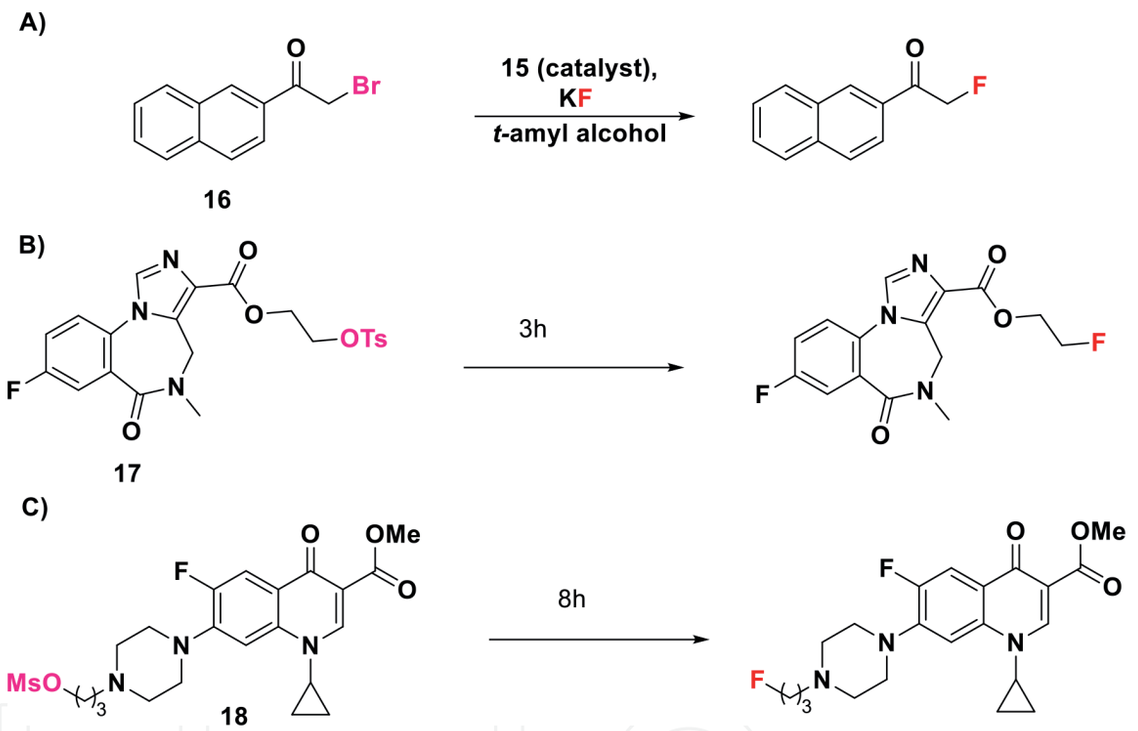


Figure 8.
Fluorination reaction by using bis-glycol substituted ILs catalyst with various leaving groups. A) acyl bromide B) tosylate C) mesylate substrates.

bi-alcohol-functionalized BFIL, having two imidazolium cations functionalized by ethylene glycol chain, showed the excellent catalytic increases in the reactivity of metal fluoride in the nucleophilic substitution among the mono-cationic convention ionic liquids. *Tert*-alcohol-funtionlaized ionic liquid not only enhances the nucleophilicity of ion but also reduces the formation of by-products alkene and ether.

The reaction of fluorination on another base-sensitive substrate of secondary alkyl tosylate using hexaehtylene glycol chain-DHIM with KF in *t*-amyl alcohol at 80°C got a better yield of the secondary fluoro-product (**Figure 10**).

2.7 Protic amine tri-*tert*-butanolamine

Shinde et al. developed novel series of protic amines, i.e. tri-*tert*-butanol amine, which can be used as catalyst or media for substitution reactions [14].

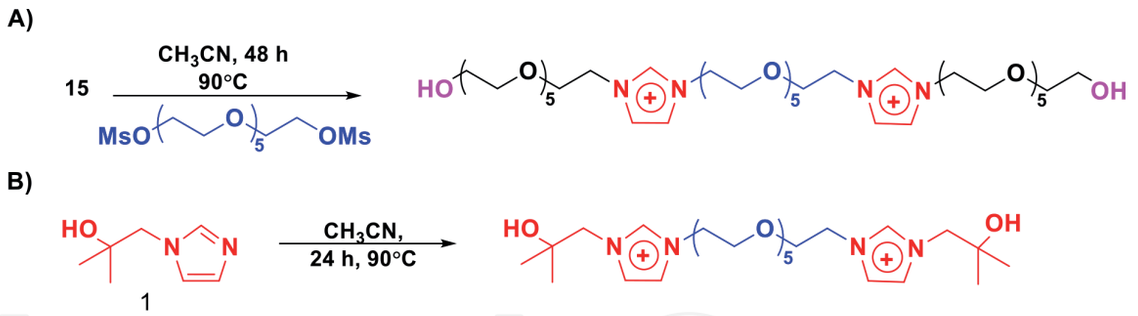


Figure 9.
Synthesis of novel bis-functionalized protic ionic liquids: (A) bis(3-hexaehtylene glycol chainyl imidazolium) dimesylate (hexaethylene glycol-DHIM) and (B) bis(2-hydroxy-2-methyl-n-propylimidazolium) dimesylate (hexaethylene glycol-D^{t}OHIM).

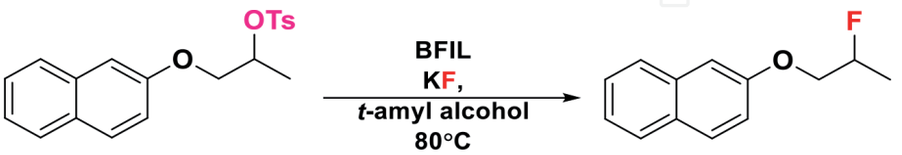


Figure 10.
Fluorination on secondary tosylate using KF with hexaehtylene glycol chain-DHIM.

Tert-butanol-functionalized amines were prepared as shown in **Figure 11**. The easy synthesis of this amine was solvent-free reaction of isobutylene oxide with respective amines to afford corresponding tri-*tert*-butanolamine [(tri-^{t}BuOH)A, 1-[Ethyl(2-hydroxy-2-methylpropyl)amino]-2-methylpropan-2-ol [(di-^{t}BuOH)EtA) and 1-(diethylamino)-2-methyl-2-propanol [(mono-^{t}BuOH)EtA]. These protic amines act as promoters with alkali metal salts in the nucleophilic fluorination of alkylsulfonates. It significantly enhances the reactivity of alkali metal salts with the minimum formation of side products (alkene, ether and alcohol) compared to conventional phase-transfer catalyst. The synergism of *tert*-alcohol and amine moiety plays a pivotal role in fluorination.

Fluorination reactions on the secondary leaving group of natural steroid substrate, cholesterol that was successfully converted into 2-fluoro-cholesterol in reasonable good yield (**Figure 12**).

The reaction of OTf-containing substrate in the presence of promoter *t*-butanolamine was much faster in giving the desired fluoro-product. It gave good substitution reactions with other leaving groups such as O-tosylate and O-nosylate as shown in **Figure 13**.

Substitution reactions with reactive substrate such as bromoacetophenone to fluoro acetophenone gave poor conversion of corresponding fluorinated product, **Figure 14**. It may be due to the *tert*-butanolamine that may react with acyl bromide and form the corresponding quaternary salts.

The reaction could be conducted in acetonitrile on a wide variety of substrates with little alkene formation observed. Further, Lee et al. studied the quantum chemical calculations of these substitution reactions and suggested that tris-*tert*-buntenolamine complexed the fluoride ion through multiple

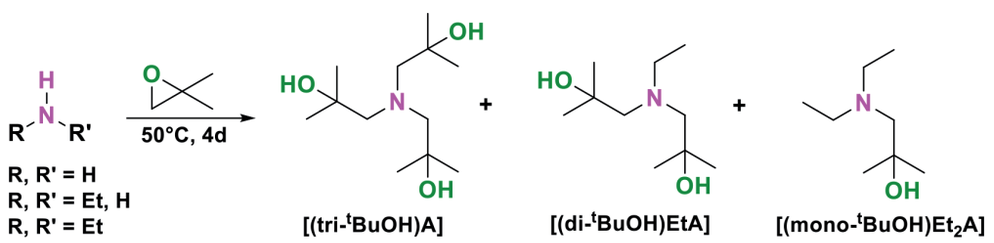


Figure 11.
Synthesis of various tert*-butanol amines.*

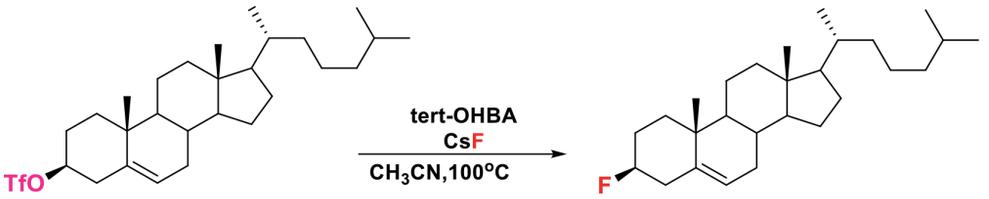


Figure 12.
Nucleophilic fluorination on secondary substrate with metal salts using t-*butanolamine.*

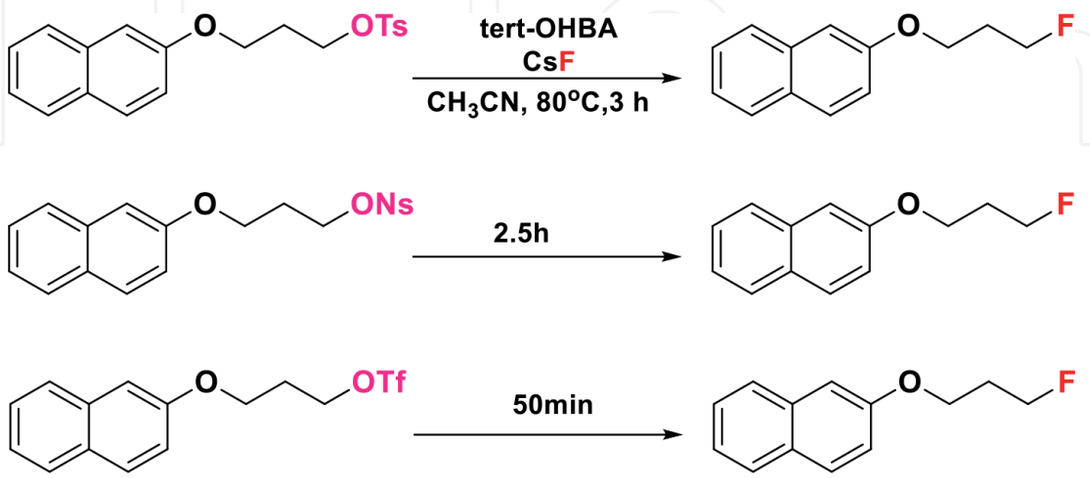


Figure 13.
Fluorination on primary substrate in the presence of t-*BuOH-amine.*

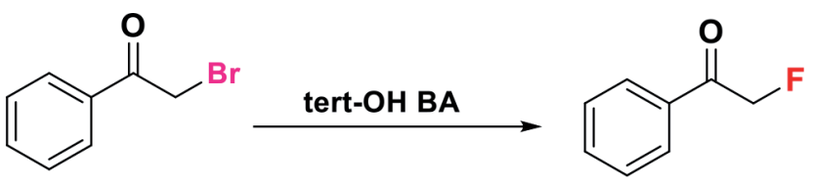


Figure 14.
Acyl bromide substitution reactions in presence of tert-*butanol amine.*

O–H···nucleophile–hydrogen bonds during the nucleophilic substitution reaction [15]. The formation of such complex did not have an effect on the reactivity of nucleophilicity and gave a selective substituted product.

3. Conclusion remark

In conclusion, the book chapter covers the recent development of protic solvents as reaction media of various substitution reactions. Aliphatic nucleophilic substitution reactions were extensively investigated in protic reaction medium and were found to be better reaction media compared to conventional aprotic solvents conditions. The protic solvents such as *tert*-amyl alcohol, *tert*-butanol, *tert*-alcohol-functionalized ionic liquid and amine are being widely used in fluorination reactions. These solvents are adopted by radiopharmaceuticals for the synthesis of value-added imaging agents for PET. The use of protic solvents is easy access and easy handling due to high-boiling points; they can be easily separated from the product because most of them are water soluble. The primary alcohol and *tert*-alcohol ionic liquids are not only used as solvents but also as promoters in various substitution reactions. These protic ionic liquids are ecofriendly and easy to synthesize and recover it after reactions.

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